## REMARKS

Applicants herewith submit a Request for Continued Examination in the above-identified patent application that had been subject to final rejection.

This Request for Continued Examination (RCE) is filed under 37 C.F.R. § 1.114. This RCE is being filed prior to the abandonment of the application, as the period for response to the Office Action has been extended until March 2, 2009 by the filing of a request for a two-month extension of time under 37 C.F.R. § 1.136(a) and the appropriate fee for this request for extension of time.

The amendments to the claims presented herein and the arguments regarding patentability applicable to the claims as amended constitute the submission required for an RCE under 37 C.F.R. § 1.114(c). The fee for a RCE under 37 C.F.R. § 1.17(e) of $405.00 (small entity) accompanies this RCE.

Therefore, this Request for Continued Examination is properly submitted, and the finality of the Office Action of September 30, 2008 should therefore be withdrawn.

Claims 10-21 are currently pending in the above-identified patent application and remain for consideration. Claims 1-9 were previously cancelled. Claims 22-23 are cancelled by this amendment. Claim 10 is amended by this amendment.

Claims 10-23 were rejected under the first paragraph of 35 U.S.C. § 112 as failing to comply with the written description requirement. This was stated to be a new matter rejection. These rejections are addressed below. By addressing these rejections, Applicants do not acquiesce in a determination that these rejections were proper or should be applied to the claims as amended.

Claims 10-23 were also rejected under the first paragraph of 35 U.S.C. § 112 for failing to comply with the enablement requirement. By addressing these rejections, Applicants again do not acquiesce in a determination that these rejections were proper or should be applied to the claims as amended.

Reexamination of the application as amended, reconsideration of the rejections, and allowance of the claims remaining for consideration are respectfully requested.

The shortened statutory period for response expires on March 2, 2009, having been extended by a two-month Request for Extension of Time filed under 37 C.F.R. § 1.136(a). Accordingly, this response is being filed in a timely manner.

## I. AMENDMENTS TO THE APPLICATION

Entry of the amendments to the application is respectfully requested. As detailed below, these amendments introduce no new matter.

Claim 10 is amended to include the limitations of previously presented claim 22, with the slight modification that "two polypeptides" is replaced with two polypeptide domains to clarify that the two domains are located in a single chimeric polypeptide. Claims 22 and 23 are therefore cancelled.

This amendment is supported by the specification, e.g., at page 4, lines 5-7, which refers specifically to "a first domain from a first isoprenoid synthase joined to a second domain from a second, heterologous isoprenoid synthase." This amendment is introduced for clarity.

This response is being filed in accordance with recently revised 37 C.F.R. § 1.121, as set forth in 68 F.R. 38611 (June 30, 2003). If the amendment is considered to

not be in compliance with recently revised 37 C.F.R. § 1.121, the Examiner is respectfully requested to contact the undersigned at his earliest possible convenience.

## II. THE REJECTION UNDER THE FIRST PARAGRAPH OF 35 U.S.C. § 112 FOR LACK OF COMPLIANCE WITH THE WRITTEN DESCRIPTION REQUIREMENT

Claims 10-23 were previously rejected under the first paragraph of 35 U.S.C. § 112, allegedly for failing to comply with the written description requirement. The Examiner stated that this was a new matter rejection; the new matter rejection is in addition to the previously-applied rejections of claims 10-19 under the first paragraph of 35 U.S.C. § 112 for lack of compliance with the written description requirement, rejections that are also now applied to newly presented claims 20-23. These rejections are addressed separately below, although they are related to some extent and the remarks below address both rejections.

As indicated above, the fact that these rejections are addressed herein does not mean that Applicants acquiesce in a determination that these rejections were proper or should be applied to the claims as amended.

### A. The New Matter Rejection of Claims 10-23

Claims 10-23 were rejected under the first paragraph of 35 U.S.C. § 112 for lack of compliance with the written description requirement. The Examiner stated that this rejection is a new matter rejection.

As detailed below, this rejection is respectfully traversed.

Specifically, the Examiner took issue with the previous assertion of Applicants that there is support for the language in claim 10 that the chimeric isoprenoid

sesquiterpene synthase polypeptide encoded by the DNA encompassed by this claim catalyzes: catalyzes: "(1) the production of at least one isoprenoid reaction product that is not produced in the absence of the second isoprenoid synthase polypeptide; or (2) the production of more than one isoprenoid reaction product in a ratio differing from the ratio of the products produced in the absence of the second isoprenoid synthase polypeptide." This assertion, according to the Examiner, was based on statements that the specification states that the chimeric isoprenoid synthase is capable of catalyzing the production of isoprenoid products that are not produced in the absence of the second domain of the second, heterologous isoprenoid synthase. However, the Examiner states that the portions of the specification to which Applicants refer recite domains of first or second isoprenoid synthase polypeptides, which, according to the Examiner, is narrower in scope than the limitations of claim 10 as previously amended. According to the Examiner, Applicants' amendment is broader in scope than the invention contemplated in the specification and thus constitutes new matter. As explained above, this language has now been clarified by amendment of claim 10 to refer to two polypeptide domains.

Additionally, according to the Examiner, there is no support in the figures or specification for "produced in the absence," in other words, for alternative (2) of the portion of claim 10 set forth above. However, the Examiner concedes that the specification does support "not produced in the absence," in other words, for alternative (1) of the portion of claim 10 set forth above. This is addressed specifically below.

A new matter rejection applied to the claims is considered to be a rejection under the first paragraph of 35 U.S.C. § 112 for lack of compliance with the written description provision of that statutory section. In re Rasmussen, 211 U.S.P.Q. 323 (C.C.P.A. 1981). Mere rephrasing of a passage or previously used terminology in the specification in the newly added claims does not constitute new matter and is not properly rejected under the first paragraph of 35 U.S.C. § 112. In re Anderson, 176 U.S.P.Q. 331 (C.C.P.A. 1973). By disclosing in a patent application a device or other subject matter, such as a chemical compound or composition, that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent

application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. In re Reynolds, 170 U.S.P.Q. 94 (C.C.P.A. 1971); In re Smythe, 178 U.S.P.Q. 279 (C.C.P.A. 1973).

Judged by these standards, there is no new matter present in the amendment of these claims, and this rejection should be withdrawn for the reasons presented below.

Firstly, the comments in the Office Action distinguishing support for recitation of different *domains* as distinguished from recitation of the production of different *products* fail to take into account the correspondence, described in the specification, between particular domains and the reactions catalyzed by particular domains that lead to different products.

Secondly, the language in the claims regarding the production by the chimeric isoprenoid sesquiterpene synthase of the present invention of products that are not produced in the absence of the second domain of the chimeric isoprenoid sesquiterpene synthase is directly supported by the specification, e.g., at page 4, lines 7-9.

Thirdly, the language in the claims regarding the production by the chimeric isoprenoid sesquiterpene synthase of the present invention of products in a different ratio is also supported by the language in the specification describing the presence and function of the ratio-determinant domain, e.g., at page 15, lines 1-12 and Figure 5. The results with, for example, CH4, CH10, CH11, and CH12 as compared with, for example, CH13 and CH14 illustrate the activity of this domain and illustrate the occurrence of the different ratio of products. This establishes that the claim language is again directly supported by the specification.

Because of the relationship between products and domains, the amendments to these claims, as well as the previously presented new claims, do not

introduce subject matter that is broader than the specification as filed and thus would be new matter. As clearly established above, this is not new matter.

Accordingly, the new matter rejection is respectfully traversed, and the Examiner is respectfully requested to withdraw it.

B. The Rejection of Claims 10-23 for Lack of Compliance with the Written Description Requirement

Claims 10-23 were rejected for lack of compliance with the written description requirement of the first paragraph of 35 U.S.C. § 112. Specifically, the Examiner stated that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

This rejection is also respectfully traversed.

As with the new matter rejection, the fact that these rejections are addressed herein does not mean that Applicants acquiesce in a determination that these rejections were proper or should be applied to the claims as amended.

Specifically, the Office Action stated that Applicants' amendments to the claims recite in claim 10 a sesquiterpene synthase and in claim 20 a DDXXD motif. However, according to the Examiner, the examples provided by the specification do not clearly describe the broadly claimed generic invention of the instant claims because there are insufficient relevant identifying characteristics.

Moreover, the Office Action stated that the assertion of Applicants that U.S. Patent No. 5,824,774 to Chappell et al. ("Chappell et al. '774") shows novel enzymes capable of synthesizing new reaction products was incorrect. According to the

Office Action, there was no mention of new reaction products in the claims or any reduction to practice of new reaction products taught in the specification. Therefore, according to the Office Action, Applicants was unable to name specifically those reaction products that are novel.

The Office Action summarized Applicants' previous arguments as follows: The product specificity domains comprised within exons 4 and 6 of wild type tobacco and henbane sesquiterpene synthase enzymes, respectively, together with the ratio domain DDXXD define Applicants' genus of chimeric sesquiterpene synthases, and that one of ordinary skill in the art would be able to identify other chimeric sesquiterpene synthases. Moreover, according to the Office Action, Applicants asserted that knowledge of the identity of the products formed by the enzymes would not have any relevance to the issue of written description because the claims are directed to nucleic acid constructs. This point shall be addressed specifically below.

Additionally, the Office Action stated that Applicants asserted that it was not required to recite each and every domain of the claimed chimeras. The Office Action further stated that Applicants have not recited in the claims the identity of any domain of the chimeric proteins other than the DDXXD ratio domain of claims 20-23, and thus Applicants have not defined the relevant characteristics of the claimed nucleic acid structure of the protein encoded therein.

Also, the Office Action stated that Applicants asserted that the work of Schalk & Croteau (M. Schalk & R. Croteau, "A Single Amino Acid Substitution (F363I) Converts the Regiochemistry of the Spearmint (-)-Limonene Hydroxylase from a C6- to a C3-Hydroxylase," Proc. Natl. Acad. Sci. USA 97: 11948-11953 (2000) ("Schalk & Croteau (2000)")) demonstrated post-filing evidence for chimeric enzymes generated by a domain-swapping. According to the Office Action, this is not made evident by Schalk & Croteau (2000), where, according to the Office Action, the authors' remarks are directed toward the involvement of specific residues and the importance of progressively placed directed mutations into a conserved region and not asymmetrically position

domains as being determinant for changes in product formation. Furthermore, according to the Office Action, the swapping of portions of the two respective enzymes analyzed by Schalk & Croteau (2000) did not follow recognized intron-exon boundaries but rather were determined as a matter of conveniently located restriction sites within the cDNA. The Office Action further emphasized that the publication date of Schalk & Croteau (2000) was well after the date of the priority claim of the above-identified application (April 12, 1996) and thus did not support Applicants' assertion that Schalk & Croteau (2000) provides a description of the broadly claimed genus of chimeric isoprenoid synthase polypeptides and polynucleotides encoding these polypeptides.

Furthermore, according to the Office Action, the work described in Schalk & Croteau (2000) did not result in the formation of "a ratio of products of the two hydroxylases." This significant point is addressed further below.

The Office Action conceded, with respect to Applicants' remarks concerning N. Dudareva et al., "(*E*)-β-Ocimene and Myrcene Synthase Genes of Floral Scent Biosynthesis in Snapdragon: Function and Expression of Three Terpene Synthase Genes of a New Terpene Synthase Subfamily," The Plant Cell 15: 1227-1241 (2003) ("Dudareva et al. (2003)"), that the claims are now directed to sesquiterpene synthases.

As detailed below, this rejection is respectfully traversed as applied to the pending claims. The specification is sufficiently detailed to meet the written description requirement under the first paragraph of 35 U.S.C. § 112 and to meet the requirements imposed by statutory and case law.

The general standard for compliance with the written description requirement has been established by case law such as In re Edwards, 196 U.S.P.Q. 465 (C.C.P.A. 1978). In In re Edwards, the Court of Customs and Patent Appeals articulated the function of the written description requirement in the following language:

> [The f]unction of [the] written description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; to comply with the description requirement, it is not necessary that the application describe the claimed invention in ipsis verbis; all that is required is that it reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him.

Id. at 567 (citations omitted). See also Vas-Cath, Inc. v. Mahurkar, 19 U.S.P.Q. 2d 1111 (Fed. Cir. 1991) (to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed).

In order to satisfy the written description requirement, it is sufficient that the specification "convey clearly to those skilled in the art the information that the applicant has invented the specific subject matter later claimed." In re Wertheim, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976). Additionally, the United States Patent and Trademark Office always has the burden of demonstrating that the applicant has failed to comply with the written description requirement. In re Salem, 193 U.S.P.Q. 513, 518 (C.C.P.A. 1987).

Again, all that is required to satisfy the written description requirement of the first paragraph of 35 U.S.C. § 112 is that the patent specification describes the claimed invention in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed subject matter, to ensure, e.g., that the invention had possession of the claimed subject matter as of the desired priority date. Regents of the University of California v. Eli Lilly & Co., 43 U.S.P.Q. 2d 1398 (Fed. Cir. 1997). In the context of nucleic acids, and by analogy, in the context of proteins encoded by nucleic acids, the recitation of structure for the claimed subject matter need not be great in order

to satisfy the written description requirement. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of a genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Regents of the University of California, 43 U.S.P.Q. 2d at 1406. Moreover, it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in the application by "other appropriate language." Id. Judged by this standard, Applicants have met the test of compliance with the written description requirement of the first paragraph of 35 U.S.C. § 112. Even if a plurality of species of nucleic acid or polypeptide molecules is claimed, there is no need to require the recitation of the complete sequence of nucleotides or amino acids for all of the species for compliance with the written description requirement of the first paragraph of 35 U.S.C. § 112. In fact, there is no requirement for the recitation of the complete sequence of even one species even if a multiplicity of species is claimed as long as the totality of the evidence establishes possession of the claimed invention.

Again, Applicants emphasize that this basic standard for compliance with the written description requirement under the first paragraph of 35 U.S.C. § 112 is satisfied by the insertion of specific language into the claims reciting the domains involved in the chimeric proteins encoded by these DNA constructs, together with the activity of the resulting chimeric proteins. There are sufficient relevant identifying characteristics to meet this standard as applied to the amended claims. These identifying characteristics are further detailed below.

Once an amino acid sequence is selected, all nucleotide sequences encoding that amino acid sequence comply with the written description requirement, because one of ordinary skill in the art can rapidly determine all corresponding nucleotide sequences. This is because the genetic code is invariant, and the codons corresponding to each amino acid are known and readily determinable by one of ordinary skill in the art. The situation is analogous to the possible rejections under the first paragraph of 35 U.S.C. § 112 for lack of enablement in this context, as considered in In re Deuel, 34

U.S.P.Q. 2d 1210, 1215 (Fed. Cir. 1995). Therefore, if sufficient detail is provided in the specification regarding the amino acid sequence of the chimeric protein, there can be no issue regarding the presence of sufficient support for nucleic acid molecules encoding the chimeric protein under the written description requirement of the first paragraph of 35 U.S.C. § 112.

With respect to the claims subject to this rejection, there is sufficient structural and functional detail to meet the standards of the written description requirement of the first paragraph of 35 U.S.C. § 112. As clearly established above, both structural and functional limitations can be considered in determining whether the specification meets the standards of the written description requirement of the first paragraph of 35 U.S.C. § 112. There is no requirement that the entire sequence of either a polynucleotide or polypeptide be recited in the specification to meet the standards of the written description requirement of the first paragraph of 35 U.S.C. § 112. Moreover, as detailed below, the functional language of the claims need also to be considered with respect to the compliance with the written description requirement of the first paragraph of 35 U.S.C. § 112.

The "Guidelines for Examination of Patent Examinations Under the 35 USC § 112 para. 1 'Written Description' Requirement," 66 Fed. Reg. 1099 (January 5, 2001) issued by the United States Patent and Trademark Office, state that the policy goals of the written description requirement are to: (i) clearly convey to the public what was invented; (ii) put the public in possession of what the applicant claims as the invention; and (iii) prevent an applicant from claiming subject matter that was not described in the specification as filed. These policy requirements are met by the pending claims.

Moreover, possession of the claimed invention can be shown by any of: (1) actual reduction to practice; (2) a "clear depiction" of the invention in detailed drawings; or (3) a description of sufficient relevant identifying characteristics. These guidelines are stated in the alternative, so that all three requirements are not required. Only one of these requirements is necessary to satisfy the standard for written description

under the first paragraph of 35 U.S.C. § 112. With regard to the pending claims, there exist both actual reduction to practice for several examples of chimeric isoprenoid sesquiterpene synthases and a depiction of sufficient relevant identifying characteristics. That is sufficient to establish the existence of possession of the claimed invention by the inventor at the time of filing. There is actual reduction to practice in terms of the production of several active chimeric synthase molecules, as set forth in Figure 4B. The actual reduction to practice goes beyond one specific embodiment. In fact, a significant number of chimeric proteins were shown to exist and be active in Figure 4B. The results recited in the specification indicate that a considerable amount of domain exchange can be performed and is consistent with the enzymatic activity of the chimeric synthases of the invention. This is shown, for example, in Figure 4B. The results shown in Figure 4B are analyzed in detail below. There is no basis for the argument that this disclosure is insufficient to provide sufficient relevant identifying characteristics, as a considerable degree of structural information is provided, not merely functional information. This structural information is implied by the organization of these chimeric proteins into domains, and the activity of the domains that is associated with specific partial enzymatic reactions.

Again, all that is required to satisfy the written description requirement of the first paragraph of 35 U.S.C. § 112 is that the patent specification describes the claimed invention in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed subject matter, to ensure, e.g., that the invention had possession of the claimed subject matter as of the desired priority date. Regents of the University of California v. Eli Lilly & Co., 43 U.S.P.Q. 2d 1398 (Fed. Cir. 1997). In the context of nucleic acids, and by analogy, in the context of proteins encoded by nucleic acids, the recitation of structure for the claimed subject matter need not be great in order to satisfy the written description requirement. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of a genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Regents of the University of California, 43 U.S.P.Q. 2d at 1406.

Moreover, it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in the application by "other appropriate language." Id. As detailed below, the functional language is within the category of "other appropriate language" such that the test of Regents of the University of California is satisfied. This functional language includes language identifying the partial reactions carried out by the two domains identified, and how those partial reactions are interrelated to produce the final product. This functional language, which characterizes the isoprenoid sesquiterpene synthases produced by translation of the nucleic acid sequences of the claims into a polypeptide sequence, clearly describes elements of the structure of those isoprenoid sesquiterpene synthases, cannot be ignored in a determination of the existence of compliance with the written description requirement of the first paragraph of 35 U.S.C. § 112.

Moreover, it is well-established that an applicant need not disclose every species encompassed by a claim. In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976). The written description requirement cannot force such a requirement, which would be unreasonable. Patents are not production documents.

There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. In re Wertheim, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976) ("we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims").

This argument is supported by other results on domain swapping. These results indicate what domains are responsible for particular steps in the enzymatic synthesis of terpenes. These domains are associated with both structural and functional features in the DNA and are correlated with the amino acid sequences encoded by particular exons in the DNA. This is in accord with the generally-accepted understanding about the significance of protein domains.

It is well understood that, in complex proteins, discrete domains are conserved evolutionarily and are associated both with specific structural features and with specific functions. Such domains can be identified and manipulated based on both structural and functional information. See J.-R. Garel, "Folding of Large Proteins: Multidomain and Multisubunit Proteins" in Protein Folding (T.E. Creighton, ed., W.H. Freeman & Co., New York, 1992), pp. 406-407, previously made of record. This illustrates the understanding of domains and how they can be used to understand protein structure and allow manipulation of multi-domain proteins while preserving the functions associated with each domain. In general, a domain is a part of the polypeptide chain of a protein molecule that forms a compact globular substructure with more interactions within itself than with other parts of the polypeptide chain. These domains not only have a compact substructure in and of themselves, but they typically carry out a partial activity or a portion of a reaction catalyzed by the protein as an enzyme. Typically, the stability of such a domain toward a denaturant such as heat, guanidinium ions, or urea is not markedly modified by the presence of the rest of the protein. This leads to the idea that domains can be duplicated or exchanged between proteins to build proteins with different functions, such as the catalysis of different enzymatic reactions, with the maintenance of the structural and functional integrity of the domains. This idea is employed in designing the constructs that encode the chimeric isoprenoid synthases incorporated in plant cells or transgenic plants in the present invention.

In many cases, the domains are contiguous or nearly contiguous with exons in a protein where the gene encoding the protein has multiple exons interrupted by non-expressed introns. This suggests that the proteins evolved by adding exons that encoded amino acid sequences having particular functions. The correspondence between exons and functional or structural domains is also employed in designing the constructs that encode the chimeric isoprenoid synthases incorporated in plant cells or transgenic plants in the present invention.

Thus, the recitation of these domains provides both structural and functional information about the claimed chimeric isoprenoid synthases. This structural

and functional information is sufficient to provide a written description of the claimed invention.

In general, the work of Applicants establishes that chimeric isoprenoid synthases that catalyze a spectrum of reaction products not obtained with naturally occurring wild-type isoprenoid synthases can be obtained. These chimeric synthases are obtained by ligating conserved functional domains of different isoprenoid synthases together, resulting in synthases that can catalyze more than one reaction in isoprenoid synthesis.

Isoprenoid synthase genes are found in a large variety of organisms including bacteria, plants, and fungi. In general, isoprenoid synthase genes, and the proteins encoded by them, demonstrate highly conserved and distinct domain regions. The individual members of the isoprenoid synthase families are multi-domain proteins that catalyze the synthesis of particular biologically active chemical compounds with a wide variety of functional groups. For any particular family member, different protein domains catalyze different steps in the overall synthesis reaction. Each family member catalyzes the synthesis of a different terpenoid compound because each member contains a different collection or arrangement of protein functional domains.

This analysis has been applied to the isoprenoid synthases. Swapping regions of the proteins that are contiguous or nearly contiguous between different isoprenoid synthases has led to the identification of functional domains responsible for the terminal enzymatic steps that catalyze the last step in the formation of specific terpenes. For example, work performed on the 5-epi-aristolochene synthase (TEAS) from *Nicotiana tabacum* (the tobacco plant) and the *Hyoscyamus muticus* (the henbane plant) vetispiradiene synthase (HVS) revealed that exon 4 of TEAS and exon 6 of HVS, respectively, were responsible for the reaction product specificity of the synthases. Combining these functional domains resulted in novel enzymes capable of synthesizing new reaction products, as shown in U.S. Patent No. 5,824,774 to Chappell et al. ("Chappell et al. '774"). The above-identified pending application is a continuation of

Application Serial No. 09/576,057, which in turn is a continuation of Application Serial No. 09/514,513, which in turn is a divisional of Application Serial No. 09/134,699, which in turn was is a continuation of Application Serial No. 08/631,341, on which Chappell et al. '774 issued.

Chappell et al. '774 clearly demonstrates that isoprenoid reaction products that are not produced other than by the chimeric isoprenoid sesquiterpene synthases disclosed therein can be produced by those chimeric isoprenoid sesquiterpene synthases. The abstract of Chappell et al. '774 reads:

> Disclosed is a chimeric isoprenoid synthase polypeptide including a first domain from a first isoprenoid synthase joined to a second domain from a second, heterologous isoprenoid synthase, whereby the chimeric isoprenoid synthase is capable of catalyzing the production of isoprenoid reaction products that are not produced in the absence of the second domain of the second, heterologous isoprenoid synthase. Also disclosed is a chimeric isoprenoid synthase polypeptide including an assymmetrically [*sic*] positioned homologous domain, whereby the chimeric isoprenoid synthase is capable of catalyzing the production of isoprenoid reaction products that are not produced when the domain is positioned at its naturally-occurring site in the isoprenoid synthase polypeptide.

Additionally, Figure 6 of Chappell et al. '774 shows a construct that can be used to produce a novel intermediate, the so-called "quiescent synthase" QH1. This "quiescent synthase" can then be further altered, as in the construct RCS shown in Figure 7 to produce a nucleic acid construct encoding casbene synthase.

The basis for the design and development of these nucleic acid constructs is the fact that different domains of these enzymes carry out different partial reactions. A substitution of a nucleic acid segment encoding one of these domains for another nucleic

acid segment encoding another of these domains that carries out a different partial reaction leads to the generation of a nucleic acid molecule that encodes a synthase that carries out a different overall reaction because of the particular sequence of partial reactions, thus yielding a novel isoprenoid compound. Many of these partial reactions constitute branch points in the overall sequence of reactions that lead to the synthesis of particular isoprenoid molecules, so that the substitution of one domain encoding an amino acid sequence that carries out one partial reaction for another domain encoding another amino acid sequence that carries out another partial reaction, when each of these two partial reactions would occur at the same branch point, leads to the generation of a nucleic acid molecule that encodes a synthase producing a novel isoprenoid compound. This strategy is employed in Chappell et al. '774.

This is explained in Chappell et al. '774, column 2, lines 18-39, as follows:

> The biosynthesis of isoprenoids such as cyclic terpenes is said to be determined by key branch point enzymes referred to as terpene synthases. The reactions [catalyzed] by terpene synthases are complex, intramolecular cyclizations that may involve several partial reactions. For example, the bioorganic rationale for the cyclization of FPP [farnesyl pyrophosphate] by two sesquiterpene synthases are shown in Fig. 3. In step 1, the initial ionization of FPP is followed by an intramolecular [electrophilic] attack between the carbon bearing the diphosphate moiety and the distal double bond to form germacrene A, a macrocyclic intermediate. Internal ring closure and formation of the eudesmane carbonium ion constitutes step 2. For tobacco 5-epi-aristolochene synthase (TEAS), the terminal step is a hydride shift, methyl migration, and deprotonation at C9 giving rise to 5-epi-aristolochene as depicted in step 3a. *Hyoscyamus muticus* vetispiradiene synthase (HVS) shares a common mechanism at steps 1 and 2, but differs from TEAS in the third partial reaction in which a ring contraction would occur due to alternative

migration of an electron pair. In each case, a monomeric protein of approximately 64 kD catalyzes the complete set of partial reactions and requires no cofactors other than $Mg^{+2}$.

Furthermore, Chappell '774 states, at column 10, lines 17-22: "The quiescent synthase is useful for providing sufficient amounts of the germacrene reaction intermediate(s) (or derivatives thereof) to confirming the chemical rationalization for the EAS and VS reactions, and produces a template chimeric synthase that may be used for the introduction of novel terminal steps in the overall synthase reaction scheme."

Similarly, Chappell '774 goes on to state, at column 10, lines 24-56:

Chimeric isoprenoid synthases are also useful for generating novel macrocyclic isoprenoids or isoprenoids having altered stereochemical properties. For example, isoprenoid synthases such as casbene synthase, a diterpene synthase which catalyzes the synthesis of a macrocyclic diterpene harboring a cyclopropyl side group, and [cadinene] synthase, a sesquiterpene synthase that catalyzes the synthesis of a bicyclic sesquiterpene, provide domains useful for engineering enzymes capable of producing macrocylic isoprenoids or isoprenoid reaction products having altered sterochemical properties. A general scheme for producing such chimeric synthases is presented in FIGS. 7 and 8.

To construct such chimeric casbene and [cadinene] synthases, quiescent amino terminal domains (and other synthase domains as necessary) are substituted with those from casbene and cadinene synthase using convenient restriction sites and PCR amplification of selected regions as described above. Sequences corresponding to the N-terminal, plastid targeting sequence of the casbene synthase are deleted in these constructs. Chimeric constructs are expressed in bacteria, bacterial lysates are examined for chimeric synthase activity, and reaction products

> are characterized as described above, for example, using argentation-TLC. Constructs supporting high levels of synthase activity in bacteria and/or activity generating reaction products which migrate with Rfs different from aristolochene and vetispiradiene standards are considered useful in the invention. Reaction products are also analyzed for their retention times by GC and subjected to GC-MS and NMR, as necessary. Those domains of casbene synthase and cadinene synthase which contribute to the synthesis of unique reaction products may also be subjected to fine detail mapping using a strategy analogous to that depicted in FIG. 4A.

Therefore, the disclosure of Chappell et al. '774 clearly supports the conclusion that novel chimeric isoprenoid synthases can be constructed that generate novel products, by following the principles described therein. These principles include the correspondence of domains with particular partial reactions and the possibility of forming novel compounds by assembling a chimeric isoprenoid synthase that carries out a particular sequence of partial reactions, with the novel compound being formed by the replacement of a domain carrying out a partial reaction located at a branch point with another domain carrying out a different partial reaction.

Therefore, the disclosure of Chappell et al. '774, which disclosed that it was possible to combine these functional domains to produce novel recombinant synthase enzymes, also supports the argument that both the written description and enablement requirements of the first paragraph of 35 U.S.C. § 112 are complied with in the above-identified pending application.

Work subsequent to the filing date of this application demonstrates that these enzymes contain conserved domains that can be reorganized in protein molecules to provide novel chimeric enzymes. The process by which these conserved domains are reorganized is known as domain swapping and is well known in the art. The process of domain swapping substantially preserves the structural and functional integrity of the domains involved in it. For example, in M. Schalk & R. Croteau, "A Single Amino Acid

Substitution (F363I) Converts the Regiochemistry of the Spearmint (-)-Limonene Hydroxylase from a C6- to a C3-Hydroxylase," Proc. Natl. Acad. Sci. 11948-11953 (2000) ("Schalk & Croteau (2000))," chimeric hydroxylases were generated using a domain-swapping process. This is completely consistent with what was known prior to that date about the function of domains in proteins and the ability to interchange domains while retaining the function of each domain.

With regard to the results of Schalk & Croteau (2000), although the existence of restriction endonuclease sites at appropriate locations was exploited in the construction of nucleic acid sequences encoding chimeric hydroxylases, a domain-swapping strategy was used to exchange domains between the two hydroxylases, the C6-hydroxylase characteristic of spearmint (*Mentha spicata*) and the C3-hydroxylase characteristic of peppermint (*M.* x *piperita*). Many of the resulting nucleic acid sequences resulting from this strategy produced functional chimeric hydroxylases when expressed in an appropriate expression system. These functional chimeric hydroxylases exhibited either C3-*trans*- or C6-*trans*-hydroxylation, although they varied to some extent in their overall activity. A similar strategy was used to exchange subdomains within one of the domains exchanged in the experiments described above with respect to the exchange of larger domains.

The results of Schalk & Croteau (2000) on domain swapping do not have less significance with respect to the practicality of domain swapping because Schalk & Croteau (2000) eventually determined a specific residue that was largely responsible by regioselectivity of these limonene hydroxylases by residue-by-residue mutagenesis. The significance of Schalk & Croteau (2000) was merely that such domain swapping was known in the art and could be readily and freely practiced. The fact that residue-by-residue mutagenesis was also employed did not alter that significance.

Schalk & Croteau (2000) was merely cited to show that the domain-swapping strategy used in some aspects of the present application was well known in the art and could be used to produce functional chimeric proteins with domains derived from

enzymes of different origins. The fact that the residue eventually found to be primarily responsible for the regioselectivity of these limonene hydroxylases was isolated by means of residue-by-residue mutagenesis does nothing to disprove the statement that the domain-swapping strategy initially employed by them was operable and could produce nucleic acid molecules encoding chimeric enzymes.

Finally, the statement that "the work of Schalk and Croteau did not result in the formation of a ratio of products of the two hydroxylases" does nothing to support a conclusion that the claims of the present application are lacking written description support in the specification or are not enabled by the specification. Schalk & Croteau (2000) did not set out to construct chimeric hydroxylases that produced multiple products as the result of the catalytic activity of a single chimeric hydroxylase. The "formation of a ratio of products of the two hydroxylases" only makes any sense when a chimeric hydroxylase enzyme is constructed that is designed to produce multiple products; in other words, when a chimeric hydroxylase or other isoprenoid synthase enzyme is constructed that has multiple, substantially self-contained, domains so that multiple products are produced, then it is reasonable to talk about the "formation of a ratio of products of the two hydroxylases." Because the domain-swapping experiments in Schalk & Croteau (2000) were not designed to construct chimeric hydroxylases such that multiple products were necessarily formed, i.e., chimeric hydroxylases with two self-contained domains where each domain contains the required amino acid sequences to catalyze a hydroxylation reaction that forms a distinct product, the failure of Schalk & Croteau (2000) to produce chimeric enzymes that form "a ratio of products of the two hydroxylases" is completely irrelevant with respect to the issue of compliance of the pending claims with the written description and enablement requirements of the first paragraph of 35 U.S.C. § 112.

Thus, it is evident from the studies of Applicants and from other work that it was known that isoprenoid synthase genes contained several highly conserved domain regions, and that domain swapping could be practiced on such genes. This work establishes that Applicants had possession of the claimed invention at the time of filing

the above-identified patent application and that one of ordinary skill in the art would recognize what is claimed was in possession of the inventors. That is all that is required to meet the written description requirement of the first paragraph of 35 U.S.C. § 112.

This is clearly not a situation in which a biomolecule sequence is described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence. Here there is a disclosed correlation between the functions of the domains and the structure of the sequence. See M.P.E.P. § 2163.

The results of Figure 4A and 4B are particularly relevant with respect to compliance with the written description requirement. The specification, at page 12, line 15, to page 14, line 9, states as follows:

> As shown in Figs. 4A-B, the dominant reaction product resulting from the expression of the tobacco TEAS gene expressed was 5-epi-aristolochene, and vetispiradiene was found to be the dominant reaction product resulting from the expression of the HVS gene. The predominant reaction products generated by the expression of CH1 and CH2 were also HVS-specific (i.e., vetispiradiene), with enzyme specific activities similar to those found for HVS that was expressed from the pBSK-HVS plasmid. These results indicated that the amino-terminal half of TEAS and HVS were functionally equivalent with respect to the HVS carboxy-terminus and do not contribute to the specificity of the reaction product. CH7, having an HVS amino terminus and a TEAS carboxy terminus, is the converse construct of CH2, and the resulting synthase activity was expected to result in expression of a TEAS-specific product (i.e., 5-epiaristolochene). Immunodetection assays revealed that synthase protein produced upon expression of CH7 was found to be of the correct size and expected abundance (data not shown); however, no enzyme activity was detected. The lack of enzyme activity indicated that

interactions between the carboxy and amino terminal portions of the protein contributed to enzyme activity. This interpretation is further supported by comparing the specific activity of the enzymes generated by the expression of the CH5 and CH6 constructs. CH5 resulted in the expression of a product having a 10-fold lower specific activity of synthase enzyme activity than the other chimeric synthases, even though the absolute level of expressed protein was similar to the other constructs (as determined by immunodetection, data not shown). Substituting an HVS carboxy-terminal region was found to restore the specific activity to the synthase enzyme that was generated by CH6.

Comparison of CH2 and CH3 chimeric synthases provided evidence for specificity of end-product formation residing within a domain of approximately 181 amino acids, corresponding to the NdeI and ClaI restriction sites within the TEAS and HVS genes. Expression of CH4 unexpectedly resulted in the production of a chimeric synthase protein capable of generating reaction products reflective of both the TEAS and HVS enzymes. We interpreted this result to indicate that amino acids 261 to 379 within the tobacco 5-aristolochene synthase are responsible for the TEAS-specific products (i.e., the region corresponding to the *Nde*I to *Hinc*II fragment of the cDNA), while amino acids 379 to 442 within the *Hyoscyamus* protein are responsible for the HVS-specific products (i.e, the region corresponding to the *Hinc*II to *Cla*I fragment of the cDNA).

Our interpretation was confirmed by evaluating the expression products of CH11 and CH12. CH11 represented the substitution of the *Nde*I to *Hinc*II fragment of the *Hyoscyamus* gene with the corresponding tobacco gene fragment, and resulted in the production of an enzyme having HVS- and TEAS-specificity. CH12 represented a substitution of the *Hinc*II to *Cla*I fragment of the tobacco gene with the corresponding *Hyoscyamus* gene fragment, and resulted in the production

of an enzyme having HVS- and TEAS- specificity. Comparing CH11 to CH13 provided a further refinement in the domain characterization of the tobacco enzyme responsible for the TEAS-specific products. The fact that CH13 was found to be a multifunctional enzyme indicated that the 81 amino acids encoded by the DNA fragment residing between the *Nde*I to *Xba*I restriction sites of the tobacco cDNA were sufficient for formation of the predominant TEAS specific products. This interpretation was confirmed by substituting the domain contained within the *NdeI/Xba*I HVS cDNA restriction fragment of CH14 with that of the TEAS gene (Fig, 4a).

Also extremely relevant is the information conveyed to one of ordinary skill in the art by Figure 5 of the above-identified application. Figure 5 is a schematic illustration showing the correspondence between exons and functional domains within isoprenoid synthases. The organization of exons within the TEAS gene is virtually identical to that of the HVS and casbene synthase genes (Fig. 5, upper diagram). The lower diagram of Figure 5 shows the alignment of functional domains to the exonic organization of the TEAS and HVS genes. The lower diagram shows that specific domains are associated with the production of 5-epi-aristolochene and vetispiradiene. An additional domain is also associated with the ratio of these products. Finally, a large portion of the amino-terminal region of these enzymes are common to at least both of the TEAS and HVS genes.

Therefore, one of ordinary skill in the art would reach the following conclusions from the data presented in the above-identified application:

(1) Specific sequences or domains are responsible for the production of the final TEAS-specific or HVS-specific products, namely 5-epi-aristolochene and vetispiradiene, respectively, and these sequences or domains have been identified and can be transferred from one protein to another to generate chimeric proteins having the desired specificity.

(2) Transferring or swapping the domains preserves their activity, thereby allowing one to construct the desired chimeric proteins.

(3) Multifunctional enzymes can be constructed by assembling the appropriate domains in the relationship shown in Figure 5.

(4) The domains correspond to exons found in the naturally-occurring genes, further strengthening the argument that the domains correspond to functional units in the naturally-occurring enzymes.

The identification of these domains, therefore, provides sufficient structural detail. This structural detail, considered together with the functional information provided and the correlation between structure and function, provides sufficient information for one of ordinary skill in the art to conclude that the inventor had possession of the claimed invention as of the filing date.

This conclusion is further supported by the results of site-directed mutagenesis, at page 15, line 14, to page 16, line 11, including Table I. These results establish that particular residues are responsible for the activity of these chimeric proteins. These residues include the DDXXD motif, and in particular the first aspartic acid residue within that motif. This further supports the structure-activity relationship that underlies the written description support present in the specification of this application.

With regard to the comments in the Office Action that there were insufficient relevant identifying characteristics, Applicants reply that sufficient identifying characteristics are in fact supplied. These identifying characteristics include conserved domains and the DDXXD domain. These identifying characteristics need not be confined to structural characteristics. They can also include functional characteristics, such as the activity of protein domains encoded by the nucleic acid sequences. These

characteristics are sufficient to enable one of ordinary skill in the art to conclude that the inventors had possession of the claimed invention, which is all that is required by the written description standard of the first paragraph of 35 U.S.C. § 112.

With regard to the comments in the Office Action that the work described in Schalk & Croteau (2000) did not result in the formation of "a ratio of products of the two hydroxylases," Applicants reply as follows: The fact that Schalk & Croteau (2000) does not result in the formation of a consistent ratio of products of two hydroxylases is merely a consequence of the fact that Schalk & Croteau (2000) was not studying chimeric isoprenoid sesquiterpene synthases in which two products are produced. The present invention clearly establishes that there is a ratio-determinant domain in these chimeric isoprenoid sesquiterpene synthases that plays a major role in determining the relative ratio of products from the two synthase domains present in these chimeric isoprenoid sesquiterpene synthases. The fact that this ratio-determinant domain was absent in Schalk & Croteau (2000) has no bearing on the conclusion that this domain exists in the nucleic acid constructs of the present invention. Schalk & Croteau (2000) is not cited for the existence of such a ratio-determinant domain and the presence or absence of such a domain in the hydroxylases described in Schalk & Croteau (2000) is irrelevant to the conclusion as to compliance with the written description requirement of the first paragraph of 35 U.S.C. § 112. There is no need to rely on Schalk & Croteau (2000) for the existence of such a ratio-determinant domain when the specification of the present application clearly describes it.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

C. The Conclusion with Respect to Both New Matter and Written Description Rejections

The conclusion with respect to both the new matter and the written description rejections is identical. The language objected to finds sufficient support in

the specification, and the specification contains sufficient detail that the only reasonable conclusion is that the inventor had possession of the claimed invention at the time of filing the application. Accordingly, the Examiner is respectfully requested to withdraw both the new matter and the written description rejections.

## III. THE REJECTION UNDER THE FIRST PARAGRAPH OF 35 U.S.C. § 112 FOR LACK OF COMPLIANCE WITH THE ENABLEMENT REQUIREMENT

Claims 10-23 were rejected under the first paragraph of 35 U.S.C. § 112, allegedly for failing to comply with the enablement requirement.

As detailed below, this rejection is also respectfully traversed.

Specifically, the Office Action stated that the claims are enabling for a nucleic acid molecule encoding a chimeric isoprenoid synthase polypeptide selected from the group consisting of: (a) the tobacco-Hyoscyamus CH4 chimeric isoprenoid synthase; (b) the tobacco-Hyoscyamus CH10 chimeric isoprenoid synthase; (c) the tobacco-Hyoscyamus CH11 chimeric isoprenoid synthase; (d) the tobacco-Hyoscyamus CH12 chimeric isoprenoid synthase; (e) the tobacco-Hyoscyamus CH13 chimeric isoprenoid synthase; and (f) the tobacco-Hyoscyamus CH14 chimeric isoprenoid synthase, as well as vectors incorporating these nucleic acid molecules and plant cells and plants transformed therewith. However, the Office Action stated that the specification did not reasonably provide enablement for DNA encoding a chimeric isoprenoid sesquiterpene synthase polypeptide, wherein said chimeric isoprenoid synthase polypeptide comprises a first isoprenoid synthase polypeptide joined to a second different isoprenoid synthase polypeptide such that the chimeric isoprenoid sesquiterpene synthase polypeptide encoded by the DNA catalyzes: (1) the production of at least one isoprenoid reaction product that is not produced in the absence of the second isoprenoid synthase polypeptide; or (2) the production of more than one isoprenoid reaction product in a ratio

differing from the ratio of the products produced in the absence of the second isoprenoid synthase polypeptide.

In reply to Applicants' previous comments with respect to this rejection, the Office Action cited Genentech, Inc. v. Novo Nordisk A/S, 42 U.S.P.Q. 2d 1001, 1005 (Fed. Cir. 1997), which stated that the disclosure of a "mere germ of an idea does not constitute [an] enabling disclosure," and that "the specification, not the knowledge of one skilled in the art," must supply the enabling aspects of the invention. According to the Office Action, the structure of the broad genus of the isoprenoid sesquiterpene synthases and their respective functions are not largely known and would require undue trial and error experimentation to determine. However, as detailed below, reliance on Genentech v. Novo Nordisk is misplaced here, inasmuch as the quantity and quality of the disclosure for the above-identified patent application is substantially greater than for the patent application whose enablement was at issue in that case. This is addressed specifically below.

Again, as with the written description rejection under the first paragraph of 35 U.S.C. § 112, the Office Action conceded, with respect to Applicants' remarks concerning Dudareva et al. (2003), that the claims are now directed to sesquiterpene synthases.

The Office Action stated that, because the publication date of Schalk & Croteau (2000) was well after the claimed priority date of the above-identified application (April 12, 1996), Schalk & Croteau (2000), as well as other unspecified references, show that the state of the art did not support Applicants' broad claim to chimeric isoprenoid sesquiterpene synthases and contradicts Applicants' assertions that the prior art and the relative skill of those in the art provide enablement for making and using what is termed :"the broadly claimed genus of chimeric isoprenoid sesquiterpene synthase polypeptides" or provide evidence that the degree of unpredictability is overcome by one of ordinary skill in the art. Specifically, the Office Action stated that the work described in Schalk & Croteau (2000) did not result in the formation of "a ratio

of products of the two hydroxylases." This significant point was addressed above with respect to the rejection under the first paragraph of 35 U.S.C. § 112 on the grounds of lack of compliance with the written description requirement and is addressed further below with respect to the rejection on the grounds of lack of enablement.

The Office Action further states that the specific examples set forth in the specification were not rejected. The Office Action rather stated that the lack of examples was what formed the basis of the rejection and that there was no teaching in the art or in Applicants' specification to support the broadly claimed genus.

The Office Action further concluded that, given the unpredictability in the art as to which domains from which plants would tolerate chimerization and produce at least a bifunctional enzyme, the breadth of the claims encompassing any plant cell comprising any number of enzymatic domains selected from a broad category of unspecified isoprenoid sesquiterpene synthases, and the lack of guidance in the specification or in the prior art, one would not know based on Applicants' disclosure which embodiments would be inoperable and predictably eliminated. Thus, according to the Office Action, undue trial and error experimentation would be needed to make and clone a multitude of non-exemplified isoprenoid synthase chimeras and to test them in a myriad of non-exemplified expression system for a multitude of non-exemplified isoprenoid sesquiterpene products. Therefore, according to the Office Action, the invention is not enabled for the full scope of the claims. The following discussion makes clear that this conclusion is not substantiated by the evidence, considering what is recited in the claims, the scope of the teachings of the disclosure, and what is known in the art.

This rejection is also respectfully traversed.

Firstly, the burden of the United States Patent and Trademark Office has not been met for this rejection. This is because the statements in the Office Action do not counter the actual examples and results cited in the specification. In particular, the specification provides, in Figure 4, the generation of chimeric isoprenoid synthases, and a

rational basis for the prediction of the activity of such chimeric isoprenoid synthases. The results shown in Figure 4 are from an actual working example, the generation of the chimeric constructs CH1-CH14. The specification further provides specific amino acid residues that play a role in catalysis, and the result of modifying those amino acid residues. This provides the basis for a structure-activity relationship that enables one of skill in the art to identify invariant residues in the domains that comprise these chimeric isoprenoid synthases. As detailed below in connection with the elucidation of the factors set forth in In re Wands, U.S.P.Q. 2d 1400 (Fed. Cir. 1988), these results are extremely useful in reducing the likelihood of unpredictability in the results and reducing the degree of experimentation required. The presence of such a structure-activity relationship is critical in establishing the existence of enablement pursuant to the first paragraph of 35 U.S.C. § 112.

It is established law with respect to enablement that the specification must be taken as being in compliance with the first paragraph of 35 U.S.C. § 112 unless there is reason to doubt the objective role of the statements contained in the specification which must be relied upon for enabling support. In re Marzocchi, 169 U.S.P.Q. 367 (C.C.P.A. 1971). No such reasons to doubt the objectivity of these statements exists here.

Moreover, properly reasoned and supported statements explaining any failure to comply with the enablement requirements of 35 U.S.C. § 112 are a requirement to properly support such a rejection. The absence of such properly reasoned and supported statements compels withdrawal of this rejection. In re Wright, 27 U.S.P.Q. 2d 1510 (Fed. Cir. 1993). The statements in the Office Action fall short of what is required under the holding of In re Wright, and reliance by the Office Action on the holding of Genentech v. Novo Nordisk does not constitute sufficient support for the rejection, as detailed below.

See also United States v. Telectronics, Inc., 8 U.S.P.Q. 2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with

information known in the art without undue experimentation."). A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 18 U.S.P.Q. 2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984).

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom. Massachusetts Institute of Technology v. A.B. Fortia, 227 U.S.P.Q. 428 (Fed. Cir. 1985). See also In re Wands, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). This test is particularly applicable in complex technologies where absolute predictability is not expected or demanded. The paradigm of such technologies is molecular biology.

Enablement can be inferred by analogy from work performed in closely related systems having closely related functions or activities. See In re Bundy, 209 U.S.P.Q. 48, 51-52 (C.C.P.A. 1981) (ruling that appellant's disclosure was sufficient to enable one skilled in the art to use the claimed analogs of naturally occurring prostaglandins even though the specification lacked any examples of specific dosages, because the specification taught that the novel prostaglandins had certain pharmacological properties and possessed activity similar to known E-type prostaglandins). This same type of reasoning by analogy is appropriate in these circumstances, because of the conserved structure and function of the domains used to construct the chimeric proteins of the present invention. The conserved structure and function of those domains was discussed in detail above with respect to the rejection on the grounds of lack of compliance with the written description requirement of the first paragraph of 35 U.S.C. § 112 and need not be further explained here. It is also well known that structure and functions of protein domains are conserved when produced after random gene fragmentation and recombination in gene shuffling. This is a general

property of protein chemistry and is frequently used to construct chimeric proteins by rational assembly of specific functional domains, as well as by other techniques such as gene shuffling. The results referred to above, particularly those shown in Figure 4 and Table I, would be interpreted by one of ordinary skill in the art as meaning that such construction was likely to be successful. There is no evidence that has been presented to suggest that such construction would be unsuccessful. The absence of such evidence, when combined with what is known in the art about the structure and function of protein domains, suggests that such construction will be successful enough of the time to meet the requirements for enablement under the first paragraph of 35 U.S.C. § 112.

The specification need not recite details of the claimed invention where one of ordinary skill in the art would consider these details obvious or well known in the art. In re Skirvan, 166 U.S.P.Q. 85 (C.C.P.A. 1970). The quantity of detail permitted to be omitted can be substantial when the state of the art is such that the detail could be readily supplied by one of ordinary skill in the art. This is true even if no working examples are furnished. In re Strahilevitz, 212 U.S.P.Q. 561 (C.C.P.A. 1982) (immunochemistry). It then follows that the presence of working examples, as provided in the specification of the present application, strengthens the case for enablement. These working examples include examples of chimeric isoprenoid synthases, including such chimeric synthases that produce two distinct products. These chimeric synthases include a ratio-determinant domain, as described above.

The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." In re Wright, 27 U.S.P.Q. 2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. In re Buchner, 18 U.S.P.Q. 2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., In re Fisher, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). An exact correlation

is not required, only a reasonable correlation. As detailed further below, this reasonable correlation is provided by the structure-activity relationships and the actual preparation of a chimeric isoprenoid synthase detailed in the present specification. This does not require recitation of the specific products produced by the chimeric isoprenoid synthase; that goes far beyond the requirements of both statute and case law. This is true even though one of ordinary skill in the art would be able, to a substantial degree of certainty, to predict those products from the information provided in the specification and general knowledge in the areas of isoprenoid chemistry, protein chemistry, and nucleic acid expression, as well as from the partial reactions catalyzed by particular domains. The pending claims do not require the specification of the particular sesquiterpene products that are produced by each chimeric isoprenoid sesquiterpene synthase within the scope of the claims. The claims are not directed to products and such a requirement would entail the provision of a degree of detail that is beyond the requirements of the patent system.

Even should considerable experimentation be required, this does not constitute "undue experimentation" if the experimentation required is routine and the worker is given sufficient guidance. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 195 U.S.P.Q. 150, 153 (C.C.P.A. 1977). Thus, the amount of experimentation that *might* be required does not give rise to a conclusion of lack of enablement. Moreover, complete reproducibility is not required to find enablement. Johns Hopkins University v. CellPro, Inc., 47 U.S.P.Q. 2d 1705 (Fed. Cir. 1998). In fact, under the holding of Johns Hopkins University, the fact that some attempts at reproducing the claimed invention fail does not lead to a conclusion of undue experimentation. In Johns Hopkins University, the invention concerned monoclonal antibodies, and attempts to reproduce the claimed invention did not uniformly result in success. The Federal Circuit held that this did not constitute undue experimentation, because a certain amount of experimentation was inherent in the Kohler-Milstein process for producing monoclonal antibodies, and a certain degree of irreproducibility was expected. Id. This decision is particularly relevant for the present application in view of the existence of a working example of a multifunctional enzyme producing two different products, namely CH13. The existence

of such a working example in this technology is strongly supportive of enablement, notwithstanding the fact that a certain degree of experimentation might be necessary to reproduce this example. This degree of experimentation is to be expected in a complex technology such as recombinant DNA technology and does not support a conclusion of lack of enablement. No evidence to suggest that this example would be irreproducible has been provided in the Office Action. As clearly emphasized above, there is considerable evidence that a significant degree of reproducibility exists.

How a teaching is set forth, by specific example or broad terminology, is not important. In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). Claims are not rejected as broader than the enabling disclosure under the first paragraph of 35 U.S.C. § 112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider them obvious. In re Skrivan, 166 U.S.P.Q. 85, 88 (C.C.P.A. 1970). Here, the conditions for generation of recombinant isoprenoid synthases would be understood by one of ordinary skill in the art and no further detail would be needed to enable one of ordinary skill in the art to reproduce the invention. These conditions would include the use of standard expression and screening techniques; there is no evidence presented in the Office Action that the use of such standard expression and screening techniques would be impractical or would introduce a degree of irreproducibility that would lead to a conclusion of lack of enablement.

The degree of unpredictability must be considered within the context of the invention and the knowledge of those skilled in the art. Even broad claims can be enabled if the subject matter of the claims is such that the unpredictability of what is actually claimed is minimized. See In re Vaeck, 20 U.S.P.Q. 2d 1438, 1444-45 (Fed. Cir. 1991) (claims directed to expression of chimeric genes in specific genera of cyanobacteria allowable even though claims were not limited to expression of genes encoding particular Bacillus proteins in view of extensive understanding in the prior art of toxicity of Bacillus proteins). The skill of those of ordinary skill in the art clearly

encompasses the preparation and use of chimeric proteins such as those recited in the claims at issue, as well as of plant cells and transgenic plants incorporating DNA encoding such chimeric proteins. This is another strong argument for enablement of the claimed invention. Again, no evidence to the contrary has been provided in the Office Action.

All that is required to provide enablement is that any mode of making and using the invention be recited in the specification. Engel Industries, Inc. v. Lockformer Corp., 20 U.S.P.Q. 2d 1300 (Fed. Cir. 1991). This test is clearly met here by the examples of particular chimeric proteins produced by domain swapping and mutagenesis described in the specification and examples of their use, when this is coupled with the knowledge of one of ordinary skill in the art of the ability to manipulate protein domains. This conclusion is reinforced by the correspondence between exons and domains shown in the specification of the above-identified application. As detailed below, the teachings of Schalk & Croteau (2000) do not contradict this correspondence.

Moreover, there is no requirement that all compositions within the scope of the claimed methods provide the same degree of efficacy or activity. In re Gardner, 177 U.S.P.Q. 396 (C.C.P.A. 1973); In re Fouche, 169 U.S.P.Q. 429 (C.C.P.A. 1971). The fact that some of these chimeric isoprenoid sesquiterpene synthases may have greater enzymatic activity than others does not mean that undue experimentation exists. Similarly, there is no requirement to specify all the possible products of these chimeric isoprenoid sesquiterpene synthases in order to satisfy the enablement requirement of the first paragraph of 35 U.S.C. § 112. As long as a product that is a sesquiterpene is produced by the catalytic activity of the chimeric enzyme, there is no further requirement to specify the product to meet the standards for enablement.

As emphasized above, the division of a complex protein into domains provides a way, well understood in the art, to manipulate the structure of such proteins to combine them into a chimeric protein while preserving their function. This is particularly significant with respect to this application, as the domains correspond to exons and thus

are likely to be associated with specific regions of the protein that carry out particular portions of the enzymatic reactions.

As is frequently the case in enablement questions, a review of the factors set forth by the Federal Circuit in In re Wands, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988), is useful. The Wands factors are: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented: (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. Id.

A review of these factors indicates that enablement is present. The conclusion is that a rejection under the first paragraph of 35 U.S.C. § 112 should be withdrawn.

Regarding Factor (1), the quantity of experimentation required is not excessive in view of the subject matter. The protein domains, and the corresponding nucleic acid sequences, involved in the construction of nucleotide sequences encoding the chimeric isoprenoid synthases of the present invention are described in detail. Methods of producing nucleic acid sequences encoding such chimeric isoprenoid synthases are also described in detail, including the generation of suitable restriction endonuclease fragments, cloning methods, expression methods, and screening methods. The same is true of proteins encoded by these nucleotide sequences; in any event, once the nucleic acid sequence encoding the protein is specified, the amino acid sequence of the protein resulting from eventual translation of the nucleic acid sequences are completely determined through the standard genetic code and is immediately known. Additionally, the invariant amino acid residues required for the catalysis of particular enzymatic reactions by these proteins are described. The ratio-determinant domain in chimeric isoprenoid sesquiterpene synthases according to the present invention is also described. The detail in the specification reduces the degree of experimentation required, as no

experimentation is required to select appropriate nucleic acid sequences or produce nucleic acid constructs encoding the chimeric isoprenoid synthases.

These teachings require little experimentation to be carried out by one of ordinary skill in the art. In particular, one of ordinary skill in the art would be able to construct nucleotide sequences corresponding to any protein sequence within the scope of the claims by the use of the genetic code coupled with standard techniques of polynucleotide synthesis, such as solid-phase nucleotide synthesis. Alternatively, the appropriate nucleic acid constructs could be assembled by using restriction endonuclease cleavage fragments, as described in the specification. Although the correspondence of exons and functional domains and the use of restriction enzymes to achieve domain swapping provides one route to the nucleotide sequences of the present invention that encode chimeric isoprenoid synthases, that is not the only possible route to such nucleotide sequences. Other routes, involving random fragmentation and recombination and not necessarily relying upon prediction of functional domain structure, are also available. These routes are described generally as "gene shuffling."

Regarding Factor (2), the amount of direction or guidance presented in the specification is substantial. This direction or guidance includes the information, as described above, with respect to the methods for the preparation of nucleic acids encoding chimeric isoprenoid synthase proteins and the resulting proteins produced by translation of the nucleic acid constructs. Moreover, as indicated above, a successful working example is present and invariant residues in isoprenoid synthase proteins are identified; these invariant residues are identified with specific partial reactions carried out in the course of the isoprenoid synthase reaction. The exact methods used are described in detail.

Regarding Factor (3), the nature of the invention is such that undue experimentation is not present, when the scope of the claimed invention is taken into account. The claimed invention, from the standpoint of enablement, is of a relatively restricted scope. Moreover, the functional language recited in all claims subject to this

rejection, as amended, must be taken into account in evaluating the existence of enablement. In re Halleck, 164 U.S.P.Q. 647 (C.C.P.A. 1970). These claims all recite that the protein encoded by the nucleic acid possesses isoprenoid synthase activity such that the chimeric isoprenoid synthase polypeptide encoded by the DNA catalyzes the production of an isoprenoid reaction product that is not produced in the absence of the second isoprenoid synthase polypeptide. This language removes non-functional proteins, and, thus, nucleotide sequences encoding non-functional proteins, from the scope of the claims. These are not claims for which a degree of extrapolation is required such that the extrapolation would lead to a conclusion of undue experimentation based on the burden placed on one of ordinary skill in the art to achieve enablement within the scope of the claimed invention. Compare In re Strahilevitz, 212 U.S.P.Q. 561 (C.C.P.A. 1982) (enablement found even though no working examples present) with In re Fisher, 166 U.S.P.Q. 18 (C.C.P.A. 1970) (no enablement for claims to an ACTH preparation having a potency of at least 1 international unit/mg, with no upper limit, when specification disclosed preparation of ACTH of potency between 1.11 and 2.30 international units/mg). Here, the scope of the protection sought is relatively circumscribed and the degree of experimentation required is minimal. The degree of experimentation required is minimized by the functional language that excludes non-functional proteins and thus nucleotide sequences encoding non-functional proteins. Again, as further emphasized below, there is no requirement that the specific products generated by any of the chimeric isoprenoid sesquiterpene synthases be recited in the claims.

Regarding Factor (4), the state of the prior art does not suggest an exceptional degree of unpredictability with respect to the activity of chimeric isoprenoid synthase activity. Although considerations relating to folding of such chimeric proteins do exist, there is sufficient secondary and tertiary structure retained on a domain-by-domain basis to make a reasonable prediction about the structure and activity of the chimeric isoprenoid sesquiterpene synthases that are incorporated into the host cells or transgenic plants of the present invention. The degree of unpredictability is further reduced by the functional limitations of these claims. Additionally, the degree of unpredictability is even further reduced by the correspondence between exons and

domains referred to above, providing one of ordinary skill in the art with a high degree of confidence that the construction of the chimeric proteins would be successful inasmuch as the domains corresponding to regions of the protein carrying out specific steps in the reaction catalyzed by the synthase enzymes.

Regarding Factor (5), the relative skill of those in the art is extremely high. This invention is directed to biochemists, microbiologists, and cell biologists, typically with a Ph.D. or other advanced degree in the relevant discipline.

Regarding Factor (6), the predictability or unpredictability of the art was discussed above. As indicated, the degree of unpredictability in the folding and, thus, the activity, of chimeric isoprenoid synthases is reduced by the existence of domains in these proteins with a largely self-contained structure. These domains are largely congruent with the exons in the naturally-occurring genes encoding for these synthases, and with regions of the protein carrying out specific steps in the reaction catalyzed by the synthase enzymes. There is no further unpredictability introduced by the transition between protein sequences and nucleotide sequences that encode the proteins. In particular, there is no evidence whatsoever to suggest that any possible sequence or arrangement of codons that encodes a polypeptide within the scope of the claim would not be functional in transcription. Again, there is no specific evidence as to the unpredictability or irreproducibility of the claimed invention presented in the Office Action.

Regarding Factor (7), the breadth of the claims does not argue for lack of enablement. The claims contain sufficient structure that one of ordinary skill in the art could predict the activity of these chimeric isoprenoid synthases, and undue experimentation would not be required. This is particularly true because of the correspondence between domains and exons referred to above. The structure recited in the claims includes the invariant residues described above. Additionally, the functional language of the claims requiring the presence of protein molecules possessing isoprenoid synthase activity must be considered in evaluating the breadth of the claims. In re Halleck, 164 U.S.P.Q. at 647.

Further regarding Factor (7), the statements in the Office Action regarding the breadth of the claims do not establish that the claims are so broad as to negate the existence of enablement. In particular, with regard to the remarks in the third full paragraph at page 7 of the Office Action, there is no significant degree of unpredictability in the art as to which domains from which plants would tolerate chimerization. The structure of these domains is known and the overall structure of the enzymes is sufficiently similar across species lines that one of ordinary skill in the art could select appropriate domains with a sufficiently high degree of probability of success. The claims do not encompass "any plant cell comprising any number of enzymatic domains selected from a broad category of unspecified isoprenoid sesquiterpene synthases." There is no language in the claims suggesting more than two enzymatic domains plus a ratio-determinant domain, and, as explained above, the structure of these domains is known and the overall structure of the enzymes is sufficiently similar across species lines to reduce uncertainty and prevent the occurrence of undue experimentation. This also applies with respect to the comment concerning the lack of guidance in the specification or in the prior art as to which domains of the isoprenoid sesquiterpene synthase enzyme family would best serve the invention.

Moreover, there is no "undue trial and error experimentation" required. The fact that a considerable number of species can be encompassed within the scope of the claims does not, in and of itself, lead to the conclusion that there is undue experimentation. Even a considerable amount of experimentation can be acceptable when the experimentation is routine. In re Colianni, 195 U.S.P.Q. at 153. Additionally, there is absolutely no evidence for "a myriad of non-exemplified expression systems." The specification describes a considerable number of expression systems and there is no evidence that any of these expression systems would be unworkable or inoperative for any DNA constructs encoding any chimeric isoprenoid sesquiterpene synthase according to the present application. Finally, the issue with respect to the existence of "a multitude of non-exemplified isoprenoid sesquiterpene products" does not lead to a conclusion of lack of enablement. The claims do not require recitation of the specific products

produced by the chimeric isoprenoid synthase. This is true even though one of ordinary skill in the art would be able, to a substantial degree of certainty, to predict those products. The claims are not directed to products and further detail is simply not required.

Additionally, regarding the language in the Office Action at page 7 with respect to the purported recitation of "any number of enzymatic domains," this issue is addressed by amendment of claim 10. There is no suggestion in the specification or claims of an infinite number of enzymatic domains. This argument does not support a conclusion of lack of enablement.

Accordingly, these factors do not support a conclusion of undue experimentation. At most, they lead to a conclusion that a certain amount of routine, non-undue experimentation is required.

In fact, the Federal Circuit itself, in Wands, found that enablement existed and that undue experimentation was not present. It held that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 8 U.S.P.Q. 2d at 1404. Wands involved monoclonal antibodies produced by hybridomas. The monoclonal antibodies had to have a certain degree of affinity toward their corresponding antigen. Of 143 hybridomas produced, only 9 were screened further, and of those 9, only four were found to fall within the scope of the claimed invention. This was sufficient to find enablement in the technology under consideration. The fact that some isoprenoid synthases encoded by polynucleotides within the scope of the claims might not have optimal catalytic activity or specificity for a particular isoprenoid synthase substrate does not suggest that the working examples do not yield enablement of the claimed invention. In any event, there is no evidence that suggests to one of ordinary skill in the art that any isoprenoid synthase encoded by any polynucleotide within the scope of the claims would be non-functional or would not have the desired catalytic activity. This evidence strongly indicates that the

amount of experimentation required to reproduce the claimed subject matter would be routine and not undue.

As long as the specification discloses at least one method for making and using the claimed invention that bears a "reasonable correlation" to the entire scope of the claimed invention, the enablement requirement of the first paragraph of 35 U.S.C. § 112 is satisfied. In re Fisher, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). That test is met here in view of the teachings of the specification, including a working example of a chimeric isoprenoid synthase that is capable of catalyzing the synthesis of both 5-epi-aristolochene and vetispiradiene.

The situation here is analogous to that in Wands. The claims are of such a scope that one of ordinary skill in the art could use the claimed invention with a reasonable probability of success. There is no requirement that all isoprenoid synthases encoded by polynucleotides within the scope of the claims of the present invention have the same degree of catalytic activity or specificity, but there is sufficient evidence that at least a significant proportion of them have the required activity. No evidence to the contrary has been presented in the Office Action.

With respect to the comments that, because Applicants have not taught what products one could expect from the myriad of possible combinations of the broadly claimed chimeric isoprenoid synthases, Applicants have not taught how to make and use the invention as broadly claimed, this does not support a conclusion of lack of enablement. As elucidated above, the claims are not directed to the products or even a method for producing products. As long as one of ordinary skill in the art could use the nucleic acids for generation of isoprenoids, that would be sufficient to satisfy the requirements of enablement under the first paragraph of 35 U.S.C. § 112. The identification of the specific combination of isoprenoids is not required for enablement here. The specification clearly provides sufficient information for one of ordinary skill in the art to make and use the claimed nucleic acid molecules and host cells incorporating them. The "effect" of the claimed invention is the generation of isoprenoids by the

synthase enzymes encoded by these nucleic acid molecules. There is no need to teach the synthesis of "any novel isoprenoid compounds" to establish enablement. That is not the standard.

The holding of Genentech, Inc. v. Novo Nordisk A/S, 42 U.S.P.Q. 2d 1001, 1005 (Fed. Cir. 1997), relied upon in the Office Action, is inapplicable here. A brief review of the facts and reasoning of Genentech v. Novo Nordisk makes this clear.

In Genentech v. Novo Nordisk, the issue of enablement arose because of a challenge to the validity of U.S. Patent No. 5,424,199 ("the '199 Patent") issued to Genentech. The single claim of that patent was directed to a method of producing a protein consisting essentially of amino acid 1-191 of human growth hormone comprising the steps of: (1) expressing in a transformant bacterium DNA coding for a human growth hormone conjugate protein consisting essentially of amino acids 1-191 of human growth hormone unaccompanied by the leader sequence of human growth hormone or other extraneous protein bound thereto and an additional amino acid sequence stated to be specifically cleavable by enzymatic action; and (2) extracellularly cleaving the conjugate protein of (1) by enzymatic action to produce the desired protein. This method is known generally as cleavable fusion expression. However, there is virtually no discussion of cleavable fusion expression in the '199 Patent. No specific examples of the production of human growth hormone or any closely homologous protein by cleavable fusion expression are provided, and there is no description of any specific cleavable conjugate protein (i.e., the conjugate protein recited in step (1) of the single method claim of the '199 Patent). The relevant portion of the specification merely describes three or perhaps four general applications for which cleavable fusion expression is considered to be generally well-suited and then names a single proteolytic enzyme that might be used as a cleavage agent, trypsin, along with sites where it cleaves. Although the specification does explicitly reference a British patent application that more fully describes the potential use of trypsin in cleavable fusion expression, in Genentech v. Novo Nordisk, the defendant, challenging the validity of the patent, pointed out that, at the time of filing the patent application that led to the '199 Patent, trypsin had been used only to digest

proteins, not to specifically and precisely cleave conjugate proteins to yield intact, useful proteins. Moreover, the British patent application referenced in the specification of the '199 Patent explicitly indicated that trypsin would not be useful for the cleavable fusion expression of arginine-containing proteins such as human growth hormone. One of ordinary skill in the art would understand that trypsin would be unsuitable for the cleavable fusion expression of an arginine-containing protein because it would also cleave at other sites within the protein and thus result in a mixture of useless peptides rather than a single cleaved product having the intact sequence of amino acid residues 1-191 of human growth hormone.

In fact, the specification of the '199 Patent was identical to the specification of an earlier Genentech patent that did not use or claim the use of cleavable fusion expression at all. The specification fails to acknowledge or discuss the problems associated with the use of trypsin in cleavable fusion expression described above.

The contrast of the factual pattern of Genentech v. Novo Nordisk with the factual pattern involved in the analysis of the specification of the present application for the presence of enablement of the pending claims could hardly be more stark. For one thing, the present application has at least one actual example of the production of chimeric isoprenoid sesquiterpene synthases. There are no missing steps or reaction conditions that need to be hypothesized or guessed at, as was the case with the '199 Patent whose validity was attacked in Genentech v. Novo Nordisk. The starting materials can be readily determined from the specification of the present application in view of the use of identifiable domains for the assembly of the chimeric isoprenoid sesquiterpene synthases. Examples of such domains are provided in the specification. By contrast, in Genentech v. Novo Nordisk, there were no examples provided of a suitable conjugate protein that could be used as a substrate for cleavable fusion expression in the '199 Patent.

Additionally, by way of contrast with the situation in Genentech v. Novo Nordisk, there is no evidence that the process of generating nucleic acid molecules

encoding a chimeric isoprenoid sesquiterpene synthase according to the present invention would be inoperative or that any step within the process would either be inoperative or would even require undue experimentation.

Moreover, there is nothing that has been cited with respect to the claims of the present application that remotely compares to the specific statements in the British published patent application cited in the specification of the '199 Patent whose validity was at issue in Genentech v. Novo Nordisk. That British published patent application specifically stated that cleavable fusion expression employing trypsin was not suitable for arginine-containing proteins, presumably because of the risk that the proteolytic enzyme trypsin would cleave at the arginine residues so that the desired product would not be obtained in intact form. There is no statement in any publication or patent application referenced in the present application or in any publication of patent application made of record during the prosecution of the present application that specifically questions the operability of the process for obtaining nucleic acid molecules that encode chimeric isoprenoid sesquiterpene synthase enzymes, or suggests that any reagents, reaction conditions, or other aspects of the process would be unworkable with these particular nucleic acid molecules or would even require undue experimentation.

Additionally, there was evidence in Genentech v. Novo Nordisk, considered by the court, that no one had been able to produce any human protein by cleavable fusion protein expression as of the filing date of the '199 Patent. This, of course, is a completely different situation than that of the present application, as there are working examples of the generation and cloning of nucleic acid segments encoding chimeric isoprenoid sesquiterpene synthase enzymes.

Unlike the situation in Genentech v. Novo Nordisk, enablement here does not rely on extremely hypothetical conjectures that were persuasively rebutted by the evidence that no one had actually been able to produce any human protein, much less human growth hormone or a close analogue to human growth hormone, by the mechanism of cleavable fusion expression. Here, in a situation exactly opposite to that of

the situation of Genentech v. Novo Nordisk, there are working examples, and the argument against enablement relies on extremely hypothetical conjectures unsupported by specific evidence that any step in the process would be inoperable or would require undue experimentation.

Accordingly, Genentech v. Novo Nordisk cannot properly be used to support a conclusion of lack of enablement.

Therefore, the Examiner is respectfully requested to withdraw the rejection of the pending claims on the grounds of lack of enablement.

## IV. CONCLUSION

In conclusion, the pending claims have written description support in the application as filed and previously-proposed amendments to these claims present no new matter. These claims are enabled so that one of ordinary skill in the art can make and use the claimed invention without undue experimentation. Accordingly, prompt allowance of these claims is respectfully requested.

If any outstanding issues remain, the Examiner is respectfully requested to telephone the undersigned at (858) 200-0581.

Respectfully submitted,

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